REMARKS

Claim 17 has been amended. Claims 17, 46, 59 to 66, 77 to 79, 87 to 89, and 95 are pending and under consideration. Support for the amendment to claim 17 is found in the specification, e.g., at page 6, line 22 to line 26.

Comment Concerning PAIR "Image File Wrapper"

In preparing the present response, applicants noted that several papers were entered into the "Image File Wrapper" of the present application on October 27, 2006. Those papers include a copy of the Amendment filed by applicants in the present application on June 9, 2006, and a copy of the Action (the Office Action mailed August 24, 2006).

Those papers were submitted on October 27, 2006, with an Information Disclosure Statement in copending U.S. Patent Application No. 09/631,613, and were not submitted in the present application. Apparently, those papers became separated from the Information Disclosure Statement, were misfiled in the present application, and were scanned into the "Image File Wrapper." Consequently, those papers entered into the "Image File Wrapper" on October 27, 2006, should not be considered a response to the outstanding Action. Further, applicants request that they be removed from the "Image File Wrapper" of the present application.

Rejection of Claim 17 Under 35 U.S.C. § 112, First Paragraph, (Written Description)

The Examiner rejected claim 17 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. See Action at page 2. Specifically, the Examiner alleged that "the functional limitation recited in the claim refers to the entire complex. Since the complex can have any number of proteins, the

functional limitation recited can be provided by any of the proteins in the complex and not necessarily by the genus of *P. furiosus* proteins encoded by polynucleotides which hybridize under the required conditions to the nucleic acid of SEQ ID NO: 70." See *id.* at page 3. Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claim 17 to include the language "wherein at least one subunit is a *P. furiosus* protein possessing nucleic acid polymerase enhancing activity." That amendment should obviate the rejection. Thus, applicants request reconsideration and withdrawal of the 35 U.S.C. § 112, First Paragraph, written description rejection.

Rejection of Claims 17 and 95 Under 35 U.S.C. § 112, First Paragraph, (Enablement)

The Examiner rejected claims 17 and 95 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. See Action at page 5. Specifically, the Examiner alleged that the specification "does not reasonably provide enablement for a protein complex comprising (1) a *P. furiosus* polypeptide of any function which is encoded by a polynucleotide which hybridizes under the specific conditions recited to the complete complement of the polynucleotide of SEQ ID NO: 70, or (2) a polypeptide having polymerase enhancing activity encoded by a polynucleotide which hybridizes under the specific conditions recited to the complete complement of the polynucleotide of SEQ ID NO: 70." See *id.* The Examiner then considered certain factors set forth in *In re Wands,* 858 F2d 731, (Fed. Cir. (1988)), and made certain allegations about those factors. Applicants will address the Examiner's contentions separately below.

In the section of the Action titled "***The breath of the claims***," the Examiner alleged that claims 17 and 95 encompass "polynucleotides which can potentially encode proteins with low structural similarity." See Action at page 6. The Examiner then considered the recited hybridization conditions in the claims and concluded that the "claimed polynucleotides can be approximately 87.5% sequence identical to the polynucleotide of SEQ ID NO: 70." See *id.* From that analysis, the Examiner concluded that "the genus of polynucleotides recited can potentially encompass polynucleotides encoding proteins which are 62% sequence identical to the polypeptide of SEQ ID NO: 71...." See *id.*

Applicants assert that even if the Examiner's contentions concerning the hybridization conditions are true, the Examiner's characterization of the polynucleotides as encoding proteins with low structural similarity is not an accurate characterization of the proteins encompassed by the claims. Specifically, the Examiner seeks to characterize proteins encoded by polynucleotides that are nearly ninety percent identical as proteins with low structural similarity.

The United States Patent and Trademark Office ("USPTO") has addressed a similar hypothetical genus of proteins and polynucleotides in the context of a written description analysis in Example 9 of the "Synopsis of Application of Written Description Guidelines" (Synopsis; available at http://www.uspto.gov/web/menu/written.pdf), which is cited in the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1101 (January 5, 2001). Example 9 of the Synopsis discusses a hypothetical claim reciting an "isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said

nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity." Synopsis at pages 35 to 36. The Synopsis states that "a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim **yield structurally similar DNAs.**" *Id.* at page 36 (emphasis added).

Like the conditions in Example 9 of the Synopsis, the conditions recited in claims 17 and 95 are stringent hybridization conditions. See the specification, e.g., at page 31, lines 32 to 33. Furthermore, the Examiner's own calculations suggest that the claims encompass polynucleotides that are 87.5% identical to the polynucleotide of SEQ ID NO: 70, which provides further evidence that the conditions are stringent. Thus, the Examiner's conclusion that claims 17 and 95 "encode proteins with low structural similarity" is inconsistent with the USPTO's position in the Synopsis that highly stringent hybridization conditions yield structurally similar DNAs. Applicants assert that claims 17 and 95, like claim 1 in Example 9 of the Synopsis, recite structurally similar polynucleotides which encode structurally similar proteins.

The Examiner also alleged that "[t]he enablement provided is not commensurate in scope with the claims due to the lack of knowledge as to the proteins required in the claimed complex such that it would have polymerase enhancing activity since the *P. furiosus* protein encoded by the recited polynucleotides can have any function, and the potentially large number of variants encompassed by the claims for which the specification provides no structure that correlates with the recited function." See Action at pages 6 to 7. Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claim 17 to include the language "wherein at least one

subunit is a *P. furiosus* protein possessing nucleic acid polymerase enhancing activity...." Thus, the Examiner's allegation that "the *P. furiosus* protein encoded by the recited polynucleotides can have any function..." is moot.

In the section of the Action titled "***The amount of direction or guidance presented and the existence of working examples***," the Examiner alleged that "the specification fails to provide any clue as to the structural elements in the polynucleotide of SEQ ID NO: 70 or the polypeptide of SEQ ID NO: 71 associated with polymerase enhancing activity or a correlation between the structures provided and the recited function." See *id.* at page 7. Applicants respectfully traverse.

In fact, the specification provides extensive guidance on the mechanism by which PEF can enhance an amplification reaction. See the specification, e.g., at page 52, line 1, to page 56, line 2. Those pages explain that dUTP can be generated in an amplification reaction by spontaneous deamination of dCTP. See the specification, e.g., at page 52, lines 16 to 18. Furthermore, the specification explains that the presence of dUTP in an amplification reaction can inhibit an amplification reaction. See the specification, e.g., at page 54, lines 7 to 9. Finally, the specification explains that the presence of PEF can prevent dUTP inhibition of an amplification reaction. See the specification, e.g., at page 54, lines 10 to 13. Thus, the specification discusses function. In addition, the specification relates that function to particular structures in SEQ ID NO: 71.

Specifically, the specification also includes sequence alignments of SEQ ID NO: 71 with related proteins. See the specification, e.g. at page 41, line 1, to page 45, line 9. Those alignments identify conserved amino acids in the sequences of the proteins.

See the specification, e.g., at page 43. The specification identifies a putative uridine binding motif in *P. furiosus* P45 and several related proteins. See the specification, e.g., at page 44, lines 1 to 17. The specification also discusses using the consensus uridine binding motif to define a protein that is a PEF. See the specification, e.g., at page 55, line 31 to page 56, line 2. Thus, the specification provides a correlation between the structure of SEQ ID NO: 71 and polymerase enhancing activity.

In the section of the Action titled "***The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art***," the Examiner alleged that:

> neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of a polypeptide having the same biological function as that of the polypeptide of SEQ ID NO: 71. In addition, the art does not provide any teaching or guidance as to (1) which amino acids in the polypeptide of SEQ ID NO: 71 can be modified and which ones need to be conserved such that one of skill in the art can make variants as recited with the same biological activity as that of the polypeptide of SEQ ID NO: 71, (2) which segments of the polypeptide of SEQ ID NO: 71 are essential for activity, and (3) the general tolerance of proteins having polymerase enhancing activity to structural modifications and the extent of such tolerance.

See *id.* at pages 7 to 8. The Examiner then cites several documents to try to support her allegation that "the art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable." See *id.* at page 7. Applicants respectfully traverse.

As discussed above, the specification does provide a correlation between structure and activity. See the specification, e.g., at page 44, lines 1 to 17. The specification also provides guidance as to which amino acids in the polypeptide of SEQ ID NO: 71 are conserved among related proteins, thus providing guidance as to which

variants are more likely to possess polymerase enhancing activity. See the specification, e.g., at page 41, line 1, to page 45, line 9. The Examiner acknowledges that "methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention." See Action at page 8. Such methods would have included knowledge of the hydropathic amino acid index, hydropathy plots, and how to use that information to make conservative amino acid substitutions, e.g., replacing a hydrophobic amino acid in a sequence with a different hydrophobic amino acid. Similarly, one of skill in the art would have understood the importance of aligning related proteins to identify conserved regions in the amino acid sequences, and non-conserved regions where amino acid changes are more likely to be tolerated without impacting the function of the resulting protein. Thus, using the guidance in the specification, one of skill in the art would have been able to predict, to some extent, which variants of SEQ ID NO. 71 are more likely to possess polymerase enhancing activity.

In the section of the Action titled "***The quantity of experimentation required to practice the claimed invention based on the teachings of the specification***," the Examiner alleged that "[w]ith regard to claim 17, one of skill in the art would have to test an infinite number of proteins to determine which ones should be included in the complex such that it would display polymerase enhancing activity since the complex as claimed does not require the *P. furiosus* protein to have that activity." See Action at page 8. As noted above, solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claim 17 to include the language "wherein at least one subunit is a *P. furiosus* protein possessing nucleic acid polymerase enhancing activity." Thus, the Examiner's allegation is moot.

The Examiner then alleged that "[w]hile enzymatic assays are well known in the art, and the skilled artisan can produce variants of the polypeptide of SEQ ID NO: 71 having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required to enable the claimed invention is not routine due to the fact that the number of species encompassed by the claims is very large." See *id.* (emphasis in original). The Examiner alleged that one of skill in the art would have to screen several billion mutants to find a single active mutant within random mutants having 62% identity to SEQ ID NO: 71. See *id.* at page 9. The Examiner alleged that "while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable mount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing." See *id.*

As applicants noted above, the specification provides guidance as to which variants of SEQ ID NO: 71 are more likely to possess polymerase enhancing activity. Thus, one of skill in the art would not have had to screen a collection of random mutants as suggested by the Examiner. Instead, one of skill in the art could screen mutants selected based on the guidance in the specification to determine which variants of SEQ ID NO: 71 possessed polymerase enhancing activity.

Moreover, even if that routine screening still involved the screening of a substantial number of mutants, that factor fails to establish non-enablement of the claims. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question

provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" See MPEP § 2164.06 citing *In re Wands* at 737 (citing *In re Angstadt,* 537 F.2d 489, 502-04 (CCPA 1976)).

In this case, the specification, not only provides guidance concerning the selection of mutants to screen as described above, but also provides guidance as to assays that can be used to screen for polypeptides possessing polymerase enhancing activity. For example, the specification describes a simple "On/Off" assay for determining whether a particular polypeptide has polymerase enhancing activity. See the specification, e.g., at page 21, line 3, to page 22, line 13, and at Figure 14. Applicants assert that one of skill in the art would have been able to perform multiple "On/Off" assays at the same time and that each "On/Off" assay could be completed in a matter of hours. Applicants assert that those experiments would not rise to the level of undue experimentation. For comparison, the MPEP provides an example of reasonable experimentation wherein studies that cost $50,000 and took six to twelve months failed to show undue experimentation. *See* MPEP § 2164.06(I).

Finally, throughout the rejection, the Examiner repeatedly focuses on an alleged lack of correlation between structure and function. Even though, in this case, the specification does provide a correlation between structure and function, applicants assert that there is no requirement of a relationship between structure and function to show enablement. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." See MPEP § 2164.01.

Thus, applicants assert that the claims are enabled. Accordingly, applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, enablement rejection of claims 17 and 95.

Double Patenting

The Examiner maintained the rejection of claims 17, 46, 59 to 66, 77 to 79, 87 to 89, and 95 under the judicially created doctrine of double patenting over certain claims of U.S. Patent No. 6,183,997. See Action at page 10, items 5 and 6.

As applicants have previously noted, without acquiescing to the rejection, if the claims are otherwise found in condition for allowance, applicants will file a terminal disclaimer.

Conclusion

If the Examiner does not consider the application to be in condition for allowance (but for the filing of a terminal disclaimer), applicants request that she call the undersigned at (650) 849-6658 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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